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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/675,927	09/29/2003	Payman Amiri	18773.004	2378

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EXAMINER	
KANTAMNENI, SHOBHA	
ART UNIT	**PAPER NUMBER**
1617	

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09/09/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/675,927	AMIRI ET AL.	
	Examiner	Art Unit	
	Shobha Kantamneni	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 July 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *75,76,78,80,82,83,88-106 and 108-112* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *NONE* is/are allowed.

6)☒ Claim(s) *75,76,78,80,82,83,88-106,108-112* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 07/30/2009 has been entered.

Applicant's amendment filed on 07/30/2009, wherein claims 75, 76, 78, 80, 82, 83, 88-101, and 104-106 have been amended.

Applicant's amendment overcomes the rejection of claims 75-76, 78, 80, 82-83, 87-106, 108-112 under 35 U.S.C. 112, first paragraph.

Claims 75, 76, 78, 80, 82, 83, 88-106, 108-112 are pending, and examined herein.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 75-76, 78, 80, 82-83, 87-106, 108-112 are rejected under 35 U.S.C. 112, first paragraph, because the specification while being enabling for a method of inhibiting Raf kinase activity in a human or animal subject suffering from a Ras/mitogen-activated protein kinase signal pathway-mediated cancer disorder selected from the group

consisting of melanoma, breast cancer, prostate cancer, lung cancer, pancreatic cancer, thyroid cancer, bladder cancer, colon cancer, liver cancer, myeloid leukemia, and villous colon adenoma in a human or animal subject, comprising administering to the human or animal subject a composition comprising an amount of a specific compound represented by formula (II), does not reasonably provide enablement for inhibiting Raf kinase activity in a human or animal subject comprising administering a composition comprising **any compound** represented by formula (II). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without **undue experimentation**. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

> (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1). The Nature of the Invention:

All of the rejected claims are drawn to an invention which pertains to a method of inhibiting Raf kinase activity in a human or animal subject comprising administering a composition comprising compound represented by formula (II).

(2). Breadth of the Claims:

The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims. The claims encompass method of inhibiting Raf kinase activity in a human or animal subject comprising administering a composition comprising any compound encompassed by the formula illustrated by the broad structure of formula (II).

What's more, the scope of the compounds claimed to be useful for the treatment method is extremely broad.

(3). Guidance of the Specification / (4). Working Examples:

Applicant provides in the specification on pages 307-309 *in vitro* assay protocol, Raf Screening in general. The specification merely recites on page 309 "Using the procedures of Examples 1401 or 1402, the compounds of Examples 1-1094 were shown to have a raf kinase inhibitory activity at an IC_{50} of less than 5 μM", out of Examples 1-1094, none of the compounds have Y = S as in instant formula (II). There is no specific data i.e raf kinase inhibitory activity data, provided for any compounds of formula (II) wherein Y is S.

There are no working examples for the method of inhibiting Raf kinase activity in a human or animal comprising administering any compounds of Formula (II).

(5). State of the Art: / (6). Predictability of the Art:

While the state of the art is relatively high with regard to a method of inhibiting Raf kinase activity in human or animal comprising administering specific compounds, the state of the art with regard to a method of inhibiting Raf kinase activity comprising administering any compounds encompassed by formula (II) is underdeveloped.

It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839 (1970). In the instant case, as discussed above, there is a vast number of compounds encompassed by the claims, the specification merely recites that the compounds of Examples 1-1094 were shown to have a raf kinase inhibitory activity at an IC_{50} of less than 5 μM, out of Examples 1-1094, none of the compounds have Y = S. It is pointed out that the compounds represented by formula (II) have wide variety of different functional groups, and will have different properties, e.g., physical, chemical, physiological effects and functions, since given the fact that any significant structural variation to a compound would be reasonably expected to alter its properties. For example, a compound with Y=O, R1=O, R2=OH in formula (II) will have different physical, chemical, physiological effects and functions such as binding abilities, solubilities than a compound with Y=S, R1, R2 form a heterocycloalkyl, and thus will have different raf kinase inhibitory activity. Also, for example A1 is heterocycloalkyl, heteroaryl etc. which can include thousands of compounds with heteroatoms such as O, S, N, and different ring size. Furthermore, there is no evidence that the compounds actually inhibit Raf kinase activity in a human or animal. Moreover, one of skill in the art

would recognize that it is highly unpredictable in regard to therapeutical effects, side effects, and especially serious toxicity that may be generated by drug-drug interactions when and/or after administering to a host (e.g., a human) any compound represented by formula II, and other anticancer agents. See "Goodman & Gilman's The Pharmacological Basis of Therapeutics" regarding possible drug-drug interactions (9th ed., 1996), page 51 in particular. Goodman & Gilman teaches that "The frequency of significant beneficial or adverse drug interactions is unknown" (see the bottom of the left column of page 51) and that "Recognition of beneficial effects and recognition of and prevention of adverse drug interactions require a thorough knowledge of the intended and possible effects of drugs that are prescribed" and that "The most important adverse drug-drug interactions occur with drugs that have serious toxicity and a low therapeutic index, such that relatively small changes in drug level can have significant adverse consequences" (see the right of page 51) (emphasis added). Thus, the compounds of formula (II) of the instant invention have different functional groups and result in different biological properties such as drug-drug interactions, formation of metabolites with different toxicities etc. Thus, the instant claimed invention as discussed above is **highly unpredictable**. The specification do not disclose which "compounds of formula (II) were tested, and do not disclose the specific Raf kinase inhibition activity of any of the compounds of formula (II), for example when Y = S in formula (II).

Moreover, the standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court of Mineral Separation v. Hyde, 242 U.S. 262, 270 (1916) which postured the question: is the experimentation needed

to practice the invention undue or unreasonable? That standard is still the one to be applied.

(7). The Quantity of Experimentation Necessary:

In order to practice the claimed invention, one of skill in the art would have to first envision a compound, a dosage for each compound, an appropriate pharmaceutical carrier, the duration of treatment, route of treatment, etc. and, in the case of human treatment, an appropriate animal model system for one of the claimed compounds. One would then need to test the compound in the model system to determine whether or not the compound is effective for inhibiting Raf kinase acitivity, and determine whether or not the compound is effective in inhibiting Raf kinase acitivity in a human or animal subject suffering from a Ras/mitogen-activated protein kinase signal pathway-mediated cancer disorder selected from the group consisting of melanoma, breast cancer, prostate cancer, lung cancer, pancreatic cancer, thyroid cancer, bladder cancer, colon cancer, liver cancer, myeloid leukemia, and villous colon adenoma. One would then also need to test the compound in the model system for side effects and toxicity at the site of pharmacological action and the therapeutic index of the drug. Thus a person of skill in the art would have to engage in **undue experimentation** to test these compounds encompassed in the instant claims and their combination with other drugs to be administered to a host employed in the claimed methods of the particular treatments herein, with no assurance of success. If unsuccessful, , one of skill in the art would have to then either envision a modification of the first pharmaceutical compound, compound dosage, duration of treatment, route of administration, etc. and appropriate

animal model system, and test the system again. Therefore, it would require undue, unpredictable experimentation to practice the claimed invention to inhibit Raf kinase activity in a human or animal subject by administration a composition comprising one of the compounds represented by formulas (II).

Genetech, 108 F.3d at 1366 states that “a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, the instant specification, does not enable the skilled artisan to make and use the claimed invention commensurate in scope with these claims.

Response to Applicant’s Arguments:

Applicant's arguments with respect to claim rejections have been considered but are not persuasive as discussed above, and those found below.

Applicant argues that “unlike Example J of the Training Materials, which only disclosed nine compounds, some of which were inoperative, all of the more than one thousand compounds of the claimed invention tested, having different functional groups, showed a Raf kinase inhibitory activity at an ICs0 of less than 5 μM. Therefore, not only are all of the tested compounds Raf inhibitors, as defined in the specification, but all of the compounds tested demonstrated activity well within the scope of this defined term.” These arguments have been considered, but not found persuasive. It is pointed out that out of Examples 1-1094, none of the compounds have Y = S. It is pointed out that the compounds represented by formula (II) have different functional groups, and will have

different properties, e.g., physical, chemical, physiological effects and functions, since given the fact that any significant structural variation to a compound would be reasonably expected to alter its properties. For example, a compound with Y=O, R1=O, R2=OH, in formula (II) will have different properties such as binding abilities, solubilities, physiological effects and function than a compound with Y=S, R1, R2 form a heterocycloalkyl, and thus will have different Raf kinase inhibitory activity. Also, in formula (II) A1 is heterocycloalkyl, heteroaryl etc. which can include thousands of compounds with heteroatoms such as O, S, N, and different ring size. In formula (II), when A1 is morpholine the resulting compound will have different properties than when A1 is thiophene. Thus, the instant claimed invention as discussed is **highly unpredictable**. The specification do not disclose which "compounds of formula (II) were tested, and do not disclose the specific Raf kinase inhibition activity of any of the compounds of formula (II), when Y = S.

Applicant argues that “As discussed supra, more than one thousand compounds of the claimed invention showed Raf kinase inhibitory activity in *in vitro* testing that satisfies the specification's definition of a "Raf inhibitor." The correlation between inhibition of Raf kinase inhibitory activity and the treatment of cancer was known in the art at the time of filing the application.” Applicant’s arguments have been considered, but not found persuasive because as discussed above out of more than one thousand compounds that showed a Raf kinase inhibitory activity at an ICs0 of less than 5 μM, none of the compounds have Y = S as in formula (II).

Applicant argues that "The '367 patent provides in vivo data demonstrating that the compound of Example 1 caused significant tumor growth inhibition or tumor regression in mice xenograft models of melanoma, colorectal carcinoma, and leukemia tumors." These arguments have been considered, but not found persuasive. It is pointed out that the compound of Example 1, and the instant compounds of formula (II) wherein Y is S have different structures and will have different properties such as binding abilities, solubilities, and Raf kinase activities. Thus, compound of Example 1 has been shown to be an inhibitor of Raf 1 kinase in human clinical trials does not provide support that all or any of the compounds of the invention will inhibit Raf kinase activity in a human or animals, since instant compounds of formula (II) is broad, and include structurally different compounds.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 75, 76, 78, 80, 82, 83, 88-106, and 108-112 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over

claims 40-42 of U.S. Application No. 12/315,779, in view of instant specification. Although the conflicting claims are not identical, they are not patentably distinct from each other. "779 does not expressly claim the employment of the compounds therein which read on instant compounds of formula (II) in the method of inhibiting Raf kinase activity. However, the employment of the compounds taught by '779 in the method of inhibiting Raf kinase activity would have been obvious in view of the instant specification because 1) instant specification teaches that it is known that Raf kinase inhibitors exhibit efficacy in inhibiting tumor cell proliferation, 2) '779 claims that the compound therein are useful in treating cancer disorder such as leukemia, breast cancer etc. See instant specification, page 3. Accordingly, one of ordinary skill in the art would have been motivated to employ the compounds taught by '779 with reasonable expectation of success inhibiting Raf kinase activity.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shobha Kantamneni whose telephone number is 571-272-2930. The examiner can normally be reached on Monday-Friday, 8am-4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, Ph.D can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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